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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

1623

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In re Patent Application of

Atty. Dkt. **1331-138**
C#/M#

von BORSTEL et al

Group Art Unit: ~~1211~~

Serial No. **08/460,186**

Examiner: ~~Kunz, G.~~ OWENS

Filed: **June 2, 1996**

Date: **October 13, 2000**

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Title: TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

☐	**NOTICE OF APPEAL** Applicant hereby appeals to the Board of Appeals from the decision dated _____ of the Examiner twice/finally rejecting claims _____ ($ 310.00)	$	0.00
☒	An appeal **BRIEF** is attached in triplicate in the pending appeal of the above-identified application ($ 310.00)	$	310.00
☐	An **ORAL HEARING** is requested under Rule 194 ($ 270.00) (due within two months after Examiner's Answer)	$	0.00
☐	Credit for fees paid in prior appeal without decision on merits	-$ (	0.00)
☐	A reply brief is attached in triplicate under Rule 193(b)		**(no fee)**
☒	Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) **($110.00/1 month**; $390.00/2 months; **$890.00/3 months**; $1390.00/4 months)	$	1890.00
	SUBTOTAL	$	2200.00
☒	Applicant is a "small entity"; enter ½ of subtotal and subtract ☐ "small entity" statement attached	-$(	1100.00)
	SUBTOTAL	$	1100.00
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	TOTAL FEE ENCLOSED	$	1100.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty.: Leonard C. Mitchard, Reg. No. 29,009

Signature: _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

In re Patent Application of

von BORSTEL et al Atty. Ref.: **1331-138**

Serial No. **08/460,186** Group: **1623**

Filed: **June 2, 1995** Examiner: ~~**Kunz, G.**~~ OWENS

For: **TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES**

* *

October 13, 2000

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

APPEAL BRIEF

Sir:

Applicant hereby appeals the Final Rejection of September 13, 1999, Paper No. 15. A Notice of Appeal was filed on March 13, 2000, along with a three month extension request.

REAL PARTY IN INTEREST

The real party in interest is Pro-Neuron, Inc., a corporation of the country of the USA.

RELATED APPEALS AND INTERFERENCES

The appellant, the undersigned, and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 1-25 are pending. Claims 26-112 are canceled. Claims 1-25 are rejected, and are the subject of the present appeal.

STATUS OF AMENDMENTS

No amendments have been filed since the date of the Final Rejection.

SUMMARY OF INVENTION

The invention relates generally to treatment of chemotherapeutic agent and antiviral agent toxicity with acylated derivatives of non-methylated pyrimidine nucleosides (page 1, second complete paragraph). These compounds are capable of attenuating damage to the hematopoietic system in animals receiving antiviral or antineoplastic chemotherapy. The invention also relates to protection of other tissues affected by antiviral or antineoplastic chemotherapy, including the gastrointestinal epithelium (page 1, last complete paragraph).

As described in the Background of the Invention section of the specification, beginning at page 2 and extending through to page 9, a major complication of cancer chemotherapy and of antiviral chemotherapy is damage to bone marrow cells or suppression of their function. Treatment of cancer patients with 5-fluorouracil (5-FU), for example, reduces the number of leukocytes and can result in enhanced susceptibility of the patients to infection. As a result, many cancer patients die of infection or other consequences of hematopoietic failure subsequent to chemotherapy (page 2, first complete paragraph).

As noted on page 5 of the application, the cytotoxicity of 5-FU derived from FT (5-fluoro-1-(tetrahydro-2-furfuryl) uracil - an orally active prodrug of 5-FU) is believed to be a result of its incorporation into nucleotide pools, where certain anabolites exert toxic effects, thereby depriving cells of thymidine for DNA synthesis. In order to inhibit this catabolism of 5-FU derived from FT, other compounds have been administered with the FT. In particular, the pyrimidine uracil inhibits the catabolism of 5-FU without inhibiting its cytotoxicity. Other pyrimidines including uridine, thymidine, thymine and cytosine are either less effective than uracil or no better in potentiating the anti-tumor efficacy of FT without unexpectedly potentiating toxicity.

Some investigators have administered pyrimidines with 5-FU in an attempt to improve the therapeutic index of this anti-neoplastic agent. However, problems of poor bioavailability after oral administration limit clinical utility of administration of cytidine as well as deoxycytidine and deoxyuridine for modulation of toxicity of chemotherapeutic agents.

As described on page 10 of the specification, the present invention provides a method for effectively preventing or treating toxic symptoms of antiviral or anticancer chemotherapy. The present invention provides compounds and methods which permit administration of high doses of the chemotherapeutic agents and of increasing blood and tissue levels of uridine and cytidine, and their corresponding deoxyribonucleosides, deoxycytidine and deoxyuridine through oral administration of a compound or compounds.

The present invention provides a method for treating toxicity due to a pyrimidine nucleoside analog. The method comprises administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside (page 42 and claim 1). Examples of such acylated derivatives of a non-methylated pyrimidine nucleoside or an acyl derivative of uridine, cytidine, deoxycytidine, or deoxyuridine (page 42 and claim 2). The pyrimidine nucleoside analogs are described at page 22 and in Claims 11-13 and

include, for example, AZT, dideoxycytidine, 5-ethyl-2'-deoxyuridine and 5-fluoroorotate.

ISSUES

The issues for consideration by the Board are:

(1) whether Claims 1-15, 18-19 and 22-25 are unpatentable over Martin et al and Sommadossi et al in view of von Borstel et al (WO 89/03837);

(2) whether Claims 16-17 and 20-21 are unpatentable over Bhalla et al in view of von Borstel and Hanzer et al; and

(3) whether Claims 1, 3-13 and 24-25 are informal under 35 U.S.C. 112, first paragraph, as not supported by an enabling disclosure.

The obviousness-type double patenting rejection has been placed in abeyance until allowable subject matter is indicated.

GROUPING OF CLAIMS

Claims 1-25 are the subject of the present appeal. Those claims stand or fall depending on the outcome of the Board's Decision

ARGUMENTS

(a) THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

The obviousness-type double patenting rejection has been placed in abeyance until it is known which of the alleged conflicting claims are allowed.

(b) THE OBVIOUSNESS REJECTIONS

Claims 1-15, 18-19 and 22-25 stand rejected under 35 USC 103 as being allegedly unpatentable over Martin et al or Sommadossi et al when taken in view of Von Borstel et al (WO 89/03837). Falcone, relied upon in the rejection dated 9-3-96, is now not mentioned in the rejection recited at page 2 of the outstanding final rejection. It is presumed reliance on Falcone has been withdrawn. The rejection is traversed for the following reasons.

The invention of the present application is directed to a method for the prevention or treatment of toxicity due to a pyrimidine nucleoside analog. The method comprises the steps of administering to an animal a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

Neither Martin nor Sommadossi suggests the use of acylated uridine or cytidine derivatives. The Examiner asserts that Von Borstel '837 would have made it obvious to a person of ordinary skill to have substituted acylated uridine or cytidine as described by Von Borstel in place of the free uridine disclosed by Martin and Sommadossi in order to increase serum and tissue levels of uridine and thereby reduce toxicity of 5-FU or AZT or any other pyrimidine nucleoside analog, regardless of the chemotherapeutic target of the nucleoside analog. Applicants disagree for the following reasons.

Martin (and others, e.g. Peters et al (Brit. J. Cancer 57:259-265, 1988)) disclose the use of uridine to reduce toxicity of 5-fluorouracil. This permits 5-FU dose escalation and a consequent net improvement in antitumor efficacy.

However, unexpected results have been obtained according to the present invention when acyl derivatives of uridine of the invention, e.g. 2', 3', 5'-triacetyluridine (TAU), are administered orally in conjunction with 5-FU. This is discussed in the specification at pages 42-44 and Example 6, and it is not seen why the applicant must present declaration evidence, as asserted by the Examiner in the first complete paragraph on page 3 of the final rejection.

Neither Martin nor Peters were able to induce even partial (50%)

regressions of the murine adenocarcinoma colon 26 with high-dose 5-FU alone at the maximum tolerated dose (100 mg/kg/week). In contrast, high-dose 5-FU in combination with oral TAU consistently results in a high incidence (60-80%) of complete regressions of established tumors.

Moreover, Kralovansky et al (Cancer Chemother Pharmacol 1993; 32:243-8), report that uridine administration after 5FU does not reduce the severity of gastrointestinal activity due to 5FU, although it does accelerate recovery from GI damage. In contrast, in human clinical trials with oral TAU administered after high dose 5FU, there is a remarkable reduction of gastrointestinal damage indicated by the no grade 3 or grade 4 mucositis or diarrhea in patients receiving up to 100 mg/m^2 5FU per week (Kelsen et al, Journal of Clinical Oncology, in press). Such toxicities are not uncommon in patients receiving normal clinical doses (500 to 600 mg/m^2 per week) of 5FU.

Thus, acyl derivatives of pyrimidine nucleosides provide unexpected benefits beyond those that have been reported for parenteral or oral administration of uridine when used to modify the toxicity and efficacy of antineoplastic pyrimidine nucleoside analogs. These same unexpected benefits are observed when TAU is administered with an inhibitor or uridine phosphorylase, e.g. benzolyoxybenzylacyclouridine, but not when the uridine

phosphorylase inhibitor alone is administered (M. el Kouni, unpublished results).

Given the deficiencies of Martin and Sommadossi, the Examiner resorts to the Von Borstel disclosure. This reference describes methods of delivering acyl derivatives of uridine or cytidine for the treatment of cardiac insufficiency, myocardial infarction, cirrhosis of the liver, cerebrovascular disorders, respiratory distress syndromes and diabetes. The specifically claimed methodology is in no way disclosed or suggested by Von Borstel, either when taken alone or in combination with Martin and/or Sommadossi. A person of ordinary skill would not therefore have been motivated to combine the references as suggested by the Examiner. Absent any such motivation to combine, it is clear that a *prima facie* case of obviousness is not generated by these references.

Martin, Sommadossi and Von Borstel taken together do not give rise to a *prima facie* case of obviousness of the methodology as claimed in claim 1 for the above-discussed reasons. The rebuttal presented above is not simply an attack on the individual references as asserted by the Examiner on pages 2 and 3 of the final rejection. The **combined** disclosures clearly do not give rise to a *prima facie* case of obviousness of the presently claimed invention. Claims 18-19 are also clearly patentably distinguished over that combination of references. Reversal of the outstanding obviousness rejection based on Martin, Sommadossi and Von

Borstel is believed to be in order, and this is requested.

Claims 16-17 and 20-21 stand rejected under 35 USC 103 as being allegedly unpatentable over Bhalla et al when taken in view of Von Borstel (WO 89/03838) and U.S. patent 4,017,606 to Hanze. That rejection is traversed for the following reasons.

Bhalla fails to describe the use of acylated deoxycytidines in place of free deoxycytidine. In an attempt to cure this deficiency, the Examiner relies on Von Borstel '838 in view of mention in that disclosure of acylated deoxycytidine.

In response, a person of ordinary skill would **not** have been motivated to arrive at the presently claimed method on the basis of the combined disclosures of Bhalla and Von Borstel. There is no suggestion in Bhalla when taken alone or in combination with Von Borstel of the methodology as claimed in this case.

Hanze is likewise deficient from the standpoint of giving rise to a *prima facie* case of obviousness against the presently claimed method. Hanze discloses pyrimidine nucleosides and nucleotides useful for inhibiting deaminating enzymes. There would have been no motivation for a person of ordinary skill to rely on this disclosure in the context of the presently claimed method.

Reversal of the outstanding obviousness rejections is now believed to be in order. Such action is respectfully requested.

(c) THE 35 USC 112, FIRST PARAGRAPH, REJECTION

The specification has been objected to, and claims 1, 3-13, and 24-25 rejected, under 35 USC 112, first paragraph, for the reasons that the specification is allegedly enabling only for claims limited to specific nucleosides listed on page 4 of the action. In response, the invention is not limited to those specific compounds recited by the Examiner. To amend the claims to recite those derivatives would be an undue limitation to the claims, and would enable third party infringers to take advantage of the invention while readily avoiding infringement. Reversal of this rejection is accordingly respectfully requested.

CONCLUSION

In conclusion it is believed that the present application is in clear condition for allowance. Reversal of the Final Rejection and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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APPENDIX

The claims on appeal are Claims 1-25. These read as follows:

1. A method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside.

2. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, deoxycytidine, or deoxyuridine.

3. A method as in claim 1 wherein said toxicity is damage to hematopoietic tissue.

4. A method as in claim 1 wherein said toxicity is damage to mucosal tissues.

5. A method as in claim 1 wherein said pyrimidine nucleoside analog is

an antineoplastic agent.

6. A method as in claim 1 wherein said pyrimidine nucleoside analog is an antiviral agent.

7. A method as in claim 1 wherein said pyrimidine nucleoside analog is an antimalarial agent.

8. A method as in claim 1 wherein said pyrimidine nucleoside analog is a cytotoxic analog of uridine.

9. A method as in claim 1 wherein said pyrimidine nucleoside analog is a cytotoxic analog of cytidine.

10. A method as in claim 1 wherein said pyrimidine nucleoside analog is an inhibitor of pyrimidine nucleotide biosynthesis.

11. A method as in claim 1 wherein said pyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil (5-FU), 5-FU prodrugs including Tegafur and 5'-deoxy-5-fluorouridine, 5-fluorouridine, 2'-deoxy-5-fluorouridine, prodrug derivatives of 5-fluorouridine or 2'-deoxy-5-fluorouridine,

fluorocytosine, trifluoromethyl-2 '-deoxyuridine, arabinosyl cytosine, prodrugs of arabinosyl cytosine, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, 6-azacytidine, N-phosphonoacetyl-L-aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, thymidine, and 3-deazauridine.

12. A method as in claim 1 wherein said pyrimidine nucleoside analog is selected from the group consisting of AZT, dideoxycytidine, 5-ethyl-2'-deoxyuridine, 5-iodo-2 '-deoxyuridine, 5-bromo-2 '-deoxyuridine, 5- methylamino-2 '-deoxyuridine, arabinosyluracil, dideoxyuridine and (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine.

13. A method as in claim 1 wherein said pyrimidine nucleoside analog is 5-fluoroorotate.

14. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is triacetyluridine.

15. A method as in claim 1 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is ethoxycarbonyluridine.

16. A method as in claim 1 wherein said acylated derivative of a non-

methylated pyrimidine nucleoside is triacetylcytidine.

17. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is diacetyldeoxycytidine.

18. A method as in claim 1 wherein said acylated derivative of a non—methylated pyrimidine nucleoside is an acylated derivative of uridine, deoxyuridine, or cytidine, and said administering step also includes administering an inhibitor of uridine phosphorylase.

19. A method as in claim 18 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclo-uridine, aminomethyl-benzylacyclouridine, aminomethyl-benzyloxybenzylacyclo-uridine, hydroxymethyl-benzylacyclouridine, and hydroxymethyl-benzyloxybenzylacyclouridine, 2,2'-anhydro-5-ethyluridine, 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, 5-benzyloxybenzylacetyl-1-[(l-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

20. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of cytidine or

deoxycytidine, and said administering step also includes administering an inhibitor of cytidine deaminase.

21. A method as in claim 20 wherein said inhibitor of cytidine deaminase is selected from the group consisting of tetrahydrouridine or tetrahydro-2'-deoxyuridine.

22. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, cytidine or deoxycytidine, and said administering step also includes administering an inhibitor of nucleoside transport.

23. A method as in claim 22 wherein said inhibitor of nucleoside transport is selected from the group consisting of dipyridamole, probenicid, lidoflazine or nitrobenzylthioinosine.

24. A method as in claim 1 wherein said administering step also includes administering an agent which enhances hematopoiesis.

25. A method as in claim 1 wherein said administering step also includes administering a compound capable of enhancing the uptake and phosphorylation

of nucleosides into cells.